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Title: Mucous membrane pemphigoid and oral blistering diseases

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5 MCQS

Learning points

- A wide spectrum of vesiculobullous disorders may present in the oral cavity.
- Early recognition, careful monitoring, and a multidisciplinary team (MDT) approach to management are essential for an optimal outcome.
- A perilesional and uninvolved buccal mucosa biopsy for direct immunofluorescence will ensure at least one tissue sample has intact epithelium and therefore establish an accurate diagnosis.
- Use of clinical disease severity scoring tools and QOL measures will confirm a clinical response to therapy.

- Serological biomarkers of disease activity may support an immunological response to therapy and are helpful for disease monitoring.
- Improvement in oral lesions is slow. Manage patient expectations accordingly.
- Optimising oral hygiene and maximising topical corticosteroid use are essential for achieving disease control.

Abstract

The autoimmune blistering disorders present with variable frequency in the oral cavity. Recognition of their key clinical features at presentation is important as there are many causes of oral ulceration. Careful history-taking, clinical examination, an understanding of pathogenesis and appropriate investigations are essential.

With the exception of the rare genodermatoses that may lead to blistering and oral ulceration, the majority of patients have an acquired disorder. These include the rare autoimmune blistering diseases mucous membrane pemphigoid (MMP), pemphigus vulgaris (PV), linear IgA disease (LAD), epidermolysis bullosa acquisita (EBA) and paraneoplastic pemphigus (PNP). Important clinical differential diagnoses include erythema multiforme (EM) which may be mistaken for PV in appearance while oral lichen planus (LP) may be indistinguishable from MMP. Angina bullosa haemorrhagica (ABH) may also present with tense haemorrhagic bullae and in the absence of diagnostic tests, requires an astute clinical diagnosis based upon the history.

Newer laboratory techniques have facilitated identification of target antigens and epitopes in the autoimmune blistering diseases particularly in MMP. Current interest is in whether these relate to clinical presentation and outcomes. There has also been recent investigation in to the use of saliva as an alternative medium to serum for the diagnosis of oral vesiculobullous lesions.

Assessment of disease severity and measurement of QOL at presentation and at subsequent follow up, is paramount to interpreting therapeutic response. Furthermore, combining these scores with serological and/or salivary biomarkers is valuable in the assessment of clinical response. Here we discuss mucous membrane pemphigoid (MMP) and its important differential diagnoses.

Introduction

MMP is a rare predominantly mucosal subepidermal blistering disorder involving the oral mucosa, conjunctiva, anogenital tissues, and upper aerodigestive tract, with occasional skin involvement. The condition is broadly heterogeneous in terms of site and severity of involvement presenting to oral medicine, ophthalmology, dermatology as well as other specialists. It generally affects the middle-aged and elderly with a predilection for Caucasian patients. It is approximately three times rarer than pemphigus vulgaris with an incidence of 2/million/year. It is characterised by linear basement-membrane zone (BMZ) autoantibody deposition with binding to a range of autoantigens including BP180, BP230, laminin 332, the β4 subunit of α6b4 integrin, and possibly the α6 subunit in a subgroup though further studies are required.[1] Type VII collagen may be associated with an MMP-like phenotype but these cases may also be classified as epidermolysis bullosa acquisita. The most frequently targeted antigen is BP180, identified in up to 75% patient sera.[2,3] In some patients presenting with widespread skin lesions alongside mucous membrane involvement, MMP may be difficult to distinguish from bullous pemphigoid (BP). However, in BP the oral lesions soon settle, and persistent mucosal lesions including ocular lesions are not seen. The propensity for scarring also distinguishes MMP from BP. It may affect the conjunctiva, nasopharynx, larynx and oesophagus but is infrequently seen in the oral mucosa due to its rapid epithelial turnover.

Oral Features

MMP is characterised by a gradual onset interspersed by acute exacerbations and remissions. In the majority, the oral mucosa is the site of onset and most frequently involved (85%) site, with other sites often additionally effected.[4,5] Intraoral sites include the gingiva (80%), buccal mucosa (58%), palate (26%), alveolar ridge (16%), tongue (15%), and lower lip (7%).[4,6] Desquamative gingivitis (DG) may range from localised gingival erythema to generalized inflammation with blistering or ulceration (Fig. 1). Gingival lesions may be indistinguishable from PV, LP, or epidermolysis bullosa acquisita (EBA) though there are characteristic differences demonstrated (Fig.2).[7] Lesions in other sites within the oral cavity appear as erythematous patches, blisters or erosions (Fig. 2). Broadly three oral phenotypes are recognised; pure gingival lesions, extra-gingival lesions or both.

Diagnosis

The diagnosis is based upon the clinical, histological, and immunopathological findings. Clinically, patients must have predominantly mucosal disease. Histology shows a subepithelial split with a mixed inflammatory infiltrate. The gold standard diagnostic test is positive direct immunofluorescence (DIF) for IgG, IgA, IgM, or C3 at the BMZ.[8] Two oral sites should ideally be sampled: a perilesional biopsy (PLB) for histology and DIF and a second normal buccal punch biopsy (NBPB) also for DIF. We have shown DIF was positive in 134/143 (93.7%) PLB samples and 129/144 (89.6%) NBPB samples (unpublished data; paper submitted). In those with pure gingival MMP, biopsy of reflected alveolar mucosa was positive in 100% (17/17). In those with predominantly ocular MMP, conjunctival positivity may be low, and an oral biopsy is recommended.[9,10]

Serum samples are valuable for identifying isotype, binding pattern and titre of circulating anti-BMZ antibodies. IgG antibodies are detected in 50–80% and/or IgA antibodies in 60%.[3,11] Detection of both IgG and IgA is associated with more severe disease.[10] Serial IgG titres correlate with disease severity.[11,12] Laminin-332 is detected in up to 20% and is associated with more severe disease and solid organ tumours in up to 30%.[13,14,15] Further testing with ELISA or immunoblotting studies may be undertaken. BIOCHIP mosaics allow polyvalent immunofluorescence tests and provide antibody profiles in a single incubation.[16] Saliva has been shown to improve the diagnostic sensitivity of serum by 30% with a combined positivity of 67%.[17]

Disease Monitoring

The Oral Disease Severity Score (ODSS) is a disease scoring tool that has been validated for MMP, PV (Fig. 3) and oral lichen planus.[18,19] The MMP disease activity index (MMPDAI) has also been proposed but awaits validation.[20] Measurement of quality of life (QoL) provides a patient-based measure to assess disease burden and monitor activity. The Oral Health Impact Profile (OHIP)[1] is the most common generic instrument used in oral medicine.[21] The Chronic Oral Mucosal Disease Questionnaire (COMDQ) is the first validated specific QoL measure to evaluate chronic conditions of the oral mucosa.[22,23,24] The Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL) is the first validated tool that allows quantitative measurement of treatment-specific impact on QoL.[25]

Treatment

There is limited evidence to guide therapy in MMP.[26,27] For mild to moderate oral disease, topical treatments may be used as mouthwashes (betamethasone 0.5mg or fluticasone propionate 400 micrograms in 10 mL of water as a 3-minute rinse) or pastes (clobetasol propionate in Orabase as a 50% mix) applied either directly or in a custom-made tray. Maintenance of good oral hygiene is paramount as plaque may compound gingival inflammation.[28] For mild to moderate disease, dapsone or tetracycline and nicotinamide are helpful. For moderate to severe disease, MMP is managed with mycophenolate mofetil or azathioprine. This may be added to a sulfa drug with or without short-term prednisolone.[29] Cyclophosphamide, IV immunoglobulin and rituximab are reserved for recalcitrant disease.

The main differential diagnoses for oral MMP

These are presented in the Table 1. Some of the key clinical features distinguishing these diseases are shown in Figure 2.

Conclusion

A wide spectrum of vesiculobullous disorders may involve the oral cavity. Early recognition, careful monitoring, and an MDT approach to management are essential.

MCQs

1. Which of the following target antigens is not involved in the pathogenesis of mucous membrane pemphigoid (MMP):
    a. BP180
    b. BP230
    c. Desmoglein 3
    d. Laminin-332
    e. β4 subunit of α6b4 integrin

2. Which of the following sites is most commonly affected in MMP?
    a. Buccal mucosa
    b. Palate
    c. Gingiva
    d. Lower lip
    e. Tongue

3. Which of the following target antigens is associated with malignancy in up to 30%?
    a. BP180
    b. BP230
    c. β4 subunit of α6b4 integrin
    d. Desmoglein 1
    e. Laminin-332

4. Which of the following drugs is not typically used in management of MMP?
    a. Dapsone
    b. Azathioprine
    c. Corticosteroids
    d. Hydroxychloroquine
    e. Topical corticosteroids

5. MMP may mimic which of the following conditions:
    a. Lichen planus
    b. Pemphigus vulgaris
    c. Linear IgA disease
    d. Epidermolysis bullosa acquisita

e. All of the above

Answers:

Question 1: C

Question 2: C

Question 3: E

Question 4: D

Question 5: E

Figures & Legends

Figure 1: MMP a) Desquamative gingivitis involving the full thickness of the attached gingiva on the buccal and labial gingiva in both arches, with focal areas of ulceration. b) Ulceration of the left buccal mucosa extending on to the palate. Yellow slough present on base of ulcers.

Figure 2: 2a) & 2b) Erosions on the palate and gingivae in pemphigus vulgaris demonstrating characteristic erythematous base to lesions and gingival margin involvement with adjacent fragile mucosa; 2c) Paraneoplastic pemphigus demonstrating a panstomatitis with yellow ulcer base and characteristic hyperplastic mucosae; 2d) Bullous lichen planus showing a deflated blister on the anterior arch of the fauces with surrounding lichenoid striae; 2e) lichen planus with characteristic full thickness desquamative gingivitis; 2f) Epidermolysis bullosa acquisita showing marginal gingival inflammation, less prominent involvement of the attached gingiva than seen in MMP, PV or LP; 2g) Erythema multiforme: haemorrhagic crusting involving the upper and lower lips. The gingiva are characteristically unaffected.

Table 1: Main differential diagnoses for MMP when affecting the oral mucosa.

(PV= pemphigus vulgaris, PNP= paraneoplastic pemphigus, LP= lichen planus, EBA= epidermolysis bullosa acquisita, LAD= linear IgA disease, EM= erythema multiforme, ABH= angina bullosa haemorrhagica, AIBD= autoimmune bullous disease, GVHD= graft versus host disease, BMZ= basement membrane zone, DIF= direct immunofluorescence, IIF= indirect immunofluorescence, IB= immunobullous, M/W= mouthwash, IVIg= intravenous immunoglobulin).

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